Summary Basis of Approval

Reference Nos.:	95-0794 (PLA Supplement) 95-1010 (ELA Supplement)
Applicant:	Genetic Systems Corporation 6565 185th Avenue NE Redmond, WA 98052
Proper Name:	Human Immunodeficiency Virus Types 1 and 2 (Synthetic Peptide)
Product Trade Name:	Genetic Systems™ HIV-1/HIV-2 Peptide EIA

I. INDICATIONS FOR USE

The Genetic Systems HIV-1/HIV-2 Peptide EIA is an *in vitro* qualitative enzyme immunoassay for the detection of circulating antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and/or Human Immunodeficiency Virus Type 2 (HIV-2) in human serum or plasma. It is indicated as a screening test for serum or plasma and as an aid in the diagnosis of infection with HIV-1 and/or HIV-2.

II. BRIEF DESCRIPTION OF TEST

The Genetic Systems HIV-1/HIV-2 Peptide EIA is manufactured using synthetic peptides derived from highly conserved, immunodominant regions of the *env* (envelope) and *pol* (polymerase) gene products for HIV-1 and HIV-2. The microwells are coated with a mixture of four peptides: *env* and *pol* sequences for both HIV-1 and HIV-2. Samples to be tested are diluted in Specimen Diluent and added to each well, and the plate is incubated and washed. If antibodies to either HIV-1 or HIV-2 are present, they bind to the adsorbed antigen and are not removed by washing. The Working Conjugate Solution, peroxidase-labeled goat anti-human immunoglobulin, is then added to the wells and will bind to the antibody-antigen complex, if present.

Unbound Conjugate is removed by a wash step. Next, Working Chromogen Solution is added to the plate and allowed to incubate. A blue or blue-green color develops in proportion to the amount of antibody that has been bound to the antigen-coated plate. The enzyme reaction is stopped by the addition of acid, which results in a color change to yellow. The optical absorbance of controls and specimens is determined with a spectrophotometer with wavelength set at 450 nm.

Components of the HIV-1/HIV-2 Peptide EIA are listed below:

- HIV-1/HIV-2 Peptide-Coated Microwell Plates: Plates containing 96 wells coated with adsorbed HIV-1 and HIV-2 peptides. Preservative: 0.1% Proclin 150™.
- Negative Control: Human serum or plasma non-reactive for HBsAg and antibodies to HIV-1, HIV-2, and HCV. Preservatives: 0.1% sodium azide and 0.01% Thimerosal.
- HIV-1 Positive Control: Human serum or plasma containing HIV-1 immunoglobulin, specific for HIV-1 by EIA; Non-reactive for HBsAg and for antibody to HCV. Preservatives: 0.1% sodium azide and 0.01% Thimerosal.
- HIV-2 Positive Control: Human serum or plasma containing HIV-2 immunoglobulin, specific for HIV-2 by EIA; Non-reactive for HBsAg and for antibody to HCV. Preservatives: 0.1% sodium azide and 0.01% Thimerosal.
- Specimen Diluent: Buffered solution with normal goat serum. Preservative: 0.1% Proclin 300
- Conjugate Concentrate: Goat anti-human IgM and IgG horseradish peroxidase-conjugated solution. Preservative: 0.01% Thimerosal.
- Conjugate Diluent: Buffered solution with protein stabilizers (normal goat serum and normal bovine serum). Preservative: 0.1% Proclin 150.
- Wash Solution Concentrate (30X): Contains sodium chloride and Tween 20.
- Chromogen Reagent: Contains tetramethylbenzidine (TMB) and dimethylsulfoxide (DMSO).
- Chromogen Diluent: Contains hydrogen peroxide, citric acid, and dimethylsulfoxide (DMSO).
- Stopping Reagent: Contains 1N H_2SO_4
- Plate Sealers: Used to cover the plates during testing.

III. MANUFACTURING AND CONTROLS

A. Manufacturing

The HIV-1/HIV-2 Peptide EIA is manufactured using four synthetic peptides derived from highly conserved, immunodominant regions of the *env* (envelope) and *pol* (polymerase) gene products for HIV-1 and HIV-2. Each lot of peptide used in the assay is evaluated for purity and functionality, both individually and in combination. Each lot of coated plates, which contains the four peptides, is tested against a panel of monoclonal antibodies and human reference sera to ensure appropriate reactivity in the HIV-1/HIV-2 Peptide EIA.

Positive and Negative Controls are prepared from human sera which are positive and negative, respectively, for antibody to HIV. The material used to make the HIV-1 Antibody Positive Control is specific for HIV-1 by EIA, and the material used to make the HIV-2 Antibody Positive Control is specific for HIV-2 by EIA. All three types of sera are non-reactive for HBsAg and anti-HCV. Positive serum is heat-treated to eliminate the infectivity of any HIV that might be present.

Raw materials intended for use in the product are subject to appropriate quality control evaluations before they are accepted for use in manufacturing. The quality of the product component is assessed at multiple stages during manufacture, using tests for product appearance and performance. Components are assembled into test kits, each lot of which is subjected to a final performance test that includes evaluation with Reference Panels prepared by the Center for Biologics Evaluation and Research (CBER) and by Genetic Systems Corporation. The panels contain serum specimens from donors negative for antibody to both HIV-1 and HIV-2, and from individuals positive for either HIV-1 or HIV-2 as well as some specimens that react with both HIV-1 and HIV-2. The performance test measures potency, reproducibility, sensitivity, and specificity. All lots of components of the Genetic Systems HIV-1/HIV-2 Peptide EIA (except for Stopping Reagent) are also monitored for bioburden (microbial load) and must meet specifications.

B. Stability Studies

The stability of the Genetic Systems HIV-1/HIV-2 Peptide EIA reagents at the recommended storage condition of 2-8°C have been verified by periodic evaluation of three (3) lots maintained under these conditions for a minimum of twelve (12) months. These studies indicate that no compromise in efficacy of kit performance is apparent under these conditions. Environmental stress studies have also been performed to determine the stability of the kit when frozen, thawed, and exposed to elevated temperature and humidity. Data from these studies support a 12-month dating period for the HIV-1/HIV-2 Peptide EIA, based on the stability of the component with the shortest dating period.

C. Methods of Validation

Product purity and potency is assured through Quality Control assessment of product appearance and performance. Product performance is assessed through laboratory evaluations comparing each lot to a control lot using panels produced by CBER and Genetic Systems Corporation. The panels contain specimens from some individuals who are negative for antibody to both HIV-1 and HIV-2, from individuals positive for either HIV-1 or HIV-2, as well as some specimens that react with both HIV-1 and HIV-2. All components of the Genetic Systems HIV-1/HIV-2 Peptide EIA, except the Stopping Reagent, are tested for bioburden levels and must meet pre-established criteria. All validation tests are performed by Genetic Systems Corporation. Three master lots of the Genetic Systems HIV-1/HIV-2 Peptide EIA have been submitted to CBER for evaluation. Each master lot of the product, along with protocols summarizing pertinent product testing, are submitted for evaluation and approval by CBER prior to release for distribution.

D. Labeling

The labeling, including container and package labels and the package circular, have been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, and 809.10 and were found to be satisfactory. The package circular for the HIV-1/HIV-2 Peptide EIA

states that the intended use of the test is for detection of HIV-1 and/or HIV-2 antibodies in serum or plasma. The product trade name, Genetic Systems™ HIV-1/HIV-2 Peptide EIA, is not known to conflict with other biologic or device trade names.

E. Establishment Inspection

An inspection of the manufacturing facilities used to produce the Genetic Systems HIV-1/HIV-2 Peptide EIA was conducted June 9, 1997 through June 13, 1997. Facilities and procedures are currently in compliance with cGMPs.

F. Environmental Assessment (EA)

A detailed Environmental Impact Analysis Report was provided in the Product License Application (Ref. No. 95-0794) for the Genetic Systems HIV-1/HIV-2 Peptide EIA. Procedures taken by Genetic Systems Corporation to assure that no adverse environmental impacts occur are listed below.

1. All human sera containing antibody to HIV-1 or HIV-2, which are used as positive controls in the HIV-1/HIV-2 Peptide EIA kit, are heat-inactivated before further manufacturing. In addition, human serum for both types of positive control and the negative control must be shown to be free of hepatitis B surface antigen and antibody to HCV before it can be used in the manufacture of this product.

2. Appropriate precautionary statements for users are included in the package insert for the product. These statements include instructions for the safe handling and disposal of hazardous materials.

3. Product shipping containers are appropriately labeled and are shipped according to applicable regulations.

Genetic Systems Corporation is in compliance with applicable emissions requirements (including occupational), at the federal, state, and local levels. There are no adverse environmental impacts anticipated as a result of this product licensure.

IV. BIOLOGICAL PRINCIPLES OF THE TEST

Genetic Systems HIV-1/HIV-2 Peptide EIA is for the detection of circulating antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and/or Human Immunodeficiency Virus Type 2 (HIV-2) in human serum or plasma, and is indicated as a screening test for serum or plasma and as an aid in the diagnosis of infection with HIV-1 and/or HIV-2. The assay is manufactured using synthetic peptides derived from highly conserved, immunodominant regions of the *env* (envelope) and *pol* (polymerase) gene products for HIV-1 and HIV-2. The microwells are coated with a mixture of four peptides: *env* and *pol* sequences for both HIV-1 and HIV-2. Samples to be tested are diluted in Specimen Diluent and added to each well, and the plate is incubated and washed. If antibodies to either HIV-1 or HIV-2 are present, they bind to the adsorbed antigen and are not removed by washing. The Working Conjugate Solution, peroxidase-labeled goat anti-human immunoglobulin, is then added to the wells and will bind to the antibody-antigen complex, if present. Unbound Conjugate is removed by a wash step.

The detection of antibodies is visualized by the addition of a Working Chromogen Solution, which is next added to the plate and allowed to incubate. A blue or blue-green color

develops in proportion to the amount of antibody that has been bound to the antigen-coated plate. The enzyme reaction is stopped by the addition of acid, which results in a color change to yellow. The optical absorbance of controls and specimens is determined with a spectrophotometer with wavelength set at 450 nm. The absorbance of each specimen is compared to the absorbance of the known positive and negative controls, and calculations of the ratio of the specimen absorbance / cutoff value determine if the sample is negative or reactive for antibodies to HIV-1/HIV-2.

V. CLINICAL DATA

A. Reproducibility

Inter-assay and intra-assay reproducibility was determined by assaying a panel of 14 specimens consisting of 6 dilutions of an HIV-1 antibody-positive specimen, 6 dilutions of an HIV-2 antibody-positive specimen, and 2 seronegative specimens. The specimens were tested 6 times on 4 different days using 3 different test kit lots at each of 7 different sites. The data were analyzed at Genetic Systems according to the National Committee for Clinical Laboratory Standards (NCCLS)[1 and 2]. The mean optical density (OD), standard deviation (SD), and percent coefficient of variation (%CV) for each panel member are listed in Table 1 below.

Table 1: Reproducibility of the Genetic Systems HIV-1/HIV-2 Peptide EIA

Inter assay Reproducibility					Intra assay Reproducibility				
Specimen	N*	Mean OD	SD[1]	%CV	Specimen	N*	Mean OD	SD[2]	%CV
1	503	0.245	0.051	20.8%	1	503	0.245	0.021	8.6%
2	500	0.712	0.139	19.5%	2	500	0.712	0.046	6.5%
3	503	0.762	0.123	16.1%	3	503	0.762	0.055	7.2%
4	504	0.446	0.092	20.6%	4	504	0.446	0.031	7.0%
5	503	1.472	0.193	13.1%	5	503	1.472	0.079	5.4%
6	502	0.440	0.079	18.0%	6	502	0.440	0.035	8.0%
7	503	1.469	0.157	10.7%	7	503	1.469	0.069	4.7%
8	497	0.066	0.020	30.3%	8	497	0.066	0.009	13.6%
9	499	0.065	0.019	29.2%	9	499	0.065	0.008	12.3%
10	500	1.966	0.121	6.2%	10	500	1.966	0.050	2.5%
11	503	0.229	0.052	22.7%	11	503	0.229	0.017	7.4%
12	499	0.127	0.030	23.6%	12	499	0.127	0.009	7.1%
13	497	0.123	0.034	27.6%	13	497	0.123	0.011	8.9%
14	502	1.917	0.159	8.3%	14	502	1.917	0.062	3.2%

* Outliers not included in statistical calculations

1. NCCLS Vol. 12 No. 4, p.33 Eq's 12 and 13
2. NCCLS Vol. 12 No. 4, p.32 Eq 11

B. Sensitivity and Specificity

1. Specificity Studies

Reactivity of Specimens from Random Blood Donors and Individuals with Other Medical Conditions Unrelated to HIV-1 or HIV-2

The results of testing on specimens from random blood donors and specimens from individuals with medical conditions unrelated to HIV-1 or HIV-2 infection are summarized in Table 2. The data include 8,266 serum and plasma samples obtained from donors at four geographically distinct locations, and 356 specimens from individuals with various medical conditions.

Table 2.
Detection of Antibodies to HIV-1 and/or HIV-2 in Random Donors and Individuals with Other Medical Conditions Unrelated to HIV Infection

Group	Results obtained with HIV-1/HIV-2 Peptide EIA				Repeatedly Reactive Specimens	
	Number tested	Non Reactive	Initially Reactive	Repeatedly Reactive	HIV-2 EIA Repeatedly Reactive	Pos. by HIV-1 Immunoblot
Random Donors Site 1[a]	2000 (100.00%)	1998 (99.90%)	2 (0.10%)	1 (0.05%)	0	0
Random Donors Site 2[a]	2250 (100.00%)	2244 (99.73%)	6 (0.27%)	2 (0.09%)	0	0
Random Donors Site 3[a]	2016 (100.00%)	2012 (99.80%)	4 (0.20%)	3 (0.15%)	0	0
Random Donors Site 4[a]	2000 (100.00%)	1998 (99.90%)	2 (0.10%)	2 (0.10%)	0	0
TOTAL	**8266 (100.00%)**	**8252 (99.83%)**	**14 (0.17%)**	**8 (0.10%)**	0	0
Bacterial/Parasitic Diseases[b]	43 (100.00%)	42 (97.67%)	1 (2.33%)	0 (0.00%)	NA	NA
Autoimmune Diseases[c]	76 (100.00%)	73 (96.05%)	3 (3.95%)	3 (3.95%)	0	0
Other Viral Diseases[d]	161 (100.00%)	159 (98.76%)	2 (1.24%)	1 (0.62%)	0	0
Malignancies[e]	23 (100.00%)	23 (100.00%)	0 (0.00%)	0 (0.00%)	NA	NA
Other Specimens[f]	53 (100.00%)	53 (100.00%)	0 (0.00%)	0 (0.00%)	NA	NA
TOTAL	**356 (100.00%)**	**350 (98.31%)**	**6 (1.69%)**	**4 (1.12%)**	0	0

a. Serum was tested at sites 2 and 4; plasma was tested at sites 1 and 3.

b. 23 toxoplasmosis; 20 RPR +

c. 15 Rheumatoid factor positive; 6 Rheumatoid arthritis; 1 Rheumatoid arthritis/Hepatitis; 2 Sjögrens; 1 SLE/Sepsis 1 SLE/Staph. aureus; 20 ANA +; 18 Elevated IgG; 12 Elevated IgM

d. 20 HBsAg +; 7 anti-HTLV-I +; 5 anti-HTLV-I/II +; 8 anti-HTLV-II +; 20 Anti-CMV +; 10 Anti-EBV +; 11 Anti-EBVCA + 10 Anti-HAV IgM +; 12 Anti-HAV Total +; 22 Anti-HCV +; 20 Anti-HSV +; 16 Anti-Rubella +

e. 1 Cancer (undefined); 1 Basal Cell; 2 Bladder; 3 Breast; 3 Colon; 1 Gall Bladder; 1 Gastric/Adeno; 2 Liver ; 1 Hepatoma; 3 Lung; 1 Pancreatic; 4 Rectal

f. 19 Multi-Transfusion; 19 Multiparous; 15 Non -viral cirrhosis [Alcohol (6); Drug (3); Primary Biliary (6)]

As shown in Table 2, 99.83% of the random donor population (n = 8,266) were initially nonreactive, 0.17% were initially reactive, and 0.10% were repeatedly reactive. Eight (57.14%) of the 14 initially reactive specimens were repeatedly reactive upon retesting. None of the repeatedly reactive specimens were positive for antibodies to HIV-1 or HIV-2 by Western blot.

Specificity of the Genetic Systems HIV-1/HIV-2 Peptide EIA was estimated from the results of screening tests in random U.S. blood and plasma donors, and determined by the following formula:

$$\frac{(\text{\# normal donor specimens} - \text{\# repeatedly reactive specimens}) \times 100}{(\text{\# normal donor specimens} - \text{\# repeatedly reactive specimens confirmed positive for antibodies to HIV})}$$

Thus, assuming a zero prevalence rate of antibodies to HIV-1 and HIV-2 in this population, the Genetic Systems HIV-1/HIV-2 Peptide EIA has an estimated specificity of (8266 - 8) x 100 / 8266 = 99.90% (95% confidence interval: 99.83-99.97%).

Six specimens from individuals with unrelated medical conditions were initially reactive. Four specimens (2 from individuals with elevated IgG, 1 from an individual with a positive ANA and 1 from an individual positive for antibodies to HTLV-I/II) were repeatedly reactive in the Genetic Systems HIV-1/HIV-2 Peptide EIA. Two specimens were negative by HIV-1 Western blot and 2 were indeterminate. All 4 specimens were nonreactive for antibody to HIV-2 when tested with a licensed HIV-2 EIA. The 2 other initially reactive specimens (1 was anti-EBV positive and 1 was positive on a serological test for syphilis) were not repeatedly reactive. None of the remaining specimens from individuals with other medical conditions were reactive in the Genetic Systems HIV-1/HIV-2 Peptide EIA.

2. Sensitivity Studies

Reactivity of Specimens Known to be Positive for Antibodies to HIV-1

The reactivity of the Genetic Systems HIV-1/HIV-2 Peptide EIA was determined by testing serum and plasma samples from patients diagnosed as having AIDS (n = 309), and from 836 individuals known to be HIV-1 antibody positive from U.S. (n = 505) and non-U.S. locations (n = 331)[a] for whom the clinical status was unknown. The samples utilized in the sensitivity evaluation of the assay were collected from diverse geographic regions, thereby increasing the likelihood of incorporating divergent strains of virus within the test population. Even though a diverse population has been tested with 100% sensitivity, it is not possible to ensure the detection of all possible divergent strains of HIV-1/HIV-2. The results of testing are shown in Table 3.

[a] Non U.S. locations included the following: Central African Republic (100); Nigeria (56); Zimbabwe (53); Australia (49); Thailand (48); France (16); Ghana (5); Nairobi (4)

Table 3: Reactivity in HIV-1 Known Positive Specimens

	Genetic Systems HIV-1/HIV-2 Peptide EIA		Licensed HIV-1/HIV-2 EIA	
Group	No. Repeatedly Reactive	(% Reactive)	No. Repeatedly Reactive	(% Reactive)
AIDS (n=309)	309	(100%)	309	(100%)
Known Positive U.S. (n = 505)	505	(100%)	505	(100%)
Known Positive Non -U.S. (n = 331)[a]	331	(100%)	331	(100%)
TOTAL	**1145**	**(100%)**	**1145**	**(100%)**

a Non U.S. locations included the following: Central African Republic (100); Nigeria (56); Zimbabwe (53); Australia (49); Thailand (48); France (16); Ghana (5); Nairobi (4)

Of the 309 diagnosed AIDS patients, 100% were repeatedly reactive with Genetic Systems HIV-1/HIV-2 Peptide EIA. Two hundred ten (210) of the AIDS specimens were positive on a licensed HIV-1 Western blot. Western blot data was not available for the remaining 99 specimens, but they were repeatedly reactive on a second licensed HIV-1/HIV-2 EIA. All 99 specimens were considered to be positive for HIV given the diagnosis of AIDS for each patient. All of the known positives from U.S. and non-U.S. locations were confirmed positive with one of three licensed HIV-1 Western blots.

The HIV-1 sensitivity of the Genetic Systems HIV-1/HIV-2 Peptide EIA was estimated from the results of testing 309 patients with AIDS. Studies demonstrated a positive test result in 309 of 309 patients for an estimated sensitivity of 100% (95% confidence interval: 99.84 to 100%).

Reactivity in Specimens from High-Risk Individuals from the United States

The results of testing for antibodies to HIV-1 and/or HIV-2 in specimens from 1080 individuals at high risk for HIV-1 infection in the United States is shown in Table 4. The numbers include 800 specimens from STD clinic patients and 280 specimens prospectively collected at a hospital emergency room in a high HIV-1 prevalence area.

All specimens were screened with one or more licensed HIV-1/HIV-2 EIAs. All specimens repeatedly reactive with Genetic Systems HIV-1/HIV-2 Peptide EIA and/or the licensed HIV-1/HIV-2 EIAs were tested with a licensed HIV-1 Western blot. Additionally, specimens repeatedly reactive with Genetic Systems HIV-1/HIV-2 Peptide EIA and/or the licensed HIV-1/HIV-2 EIA were tested with a licensed HIV-2 EIA. If the HIV-1 Western blot was negative or indeterminate and the HIV-2 EIA was repeatedly reactive, the specimen was tested by an investigational HIV-2 Western blot.

Table 4: Reactivity in Specimens from High-Risk Individuals from the United States

Group	No. Tested	Genetic Systems HIV-1/HIV-2 Peptide EIA Repeatedly Reactive	No. RR on one or more Licensed HIV-1/HIV-2 EIA	No. Pos. by HIV-1 Western blot
STD Clinic	800	33 (4.1%)	38	28 (3.5%)
E.R. Patients	280	36 (12.9%)	36	31 (11.1%)
Total	1080	69 (6.4%)[a]	74[a]	59 (5.5%)

[a] Sixty-two (62) specimens were repeatedly reactive on both the Genetic Systems HIV-1/HIV-2 Peptide EIA and one or more licensed HIV-1/HIV-2 EIAs.

All 59 specimens that were positive by HIV-1 Western blot and repeatedly reactive on a licensed HIV-1/HIV-2 EIA were also repeatedly reactive on the Genetic Systems HIV-1/HIV-2 Peptide EIA.

A total of 81 specimens were additionally tested with a licensed HIV-2 EIA (62 specimens repeatedly reactive on Genetic Systems HIV-1/HIV-2 Peptide EIA and one or more licensed HIV-1/HIV-2 EIAs; 7 specimens repeatedly reactive on the Genetic Systems HIV-1/HIV-2 Peptide EIA only; 12 specimens repeatedly reactive on one or more licensed EIAs only). Of the 81 specimens tested with a licensed HIV-2 EIA, 42 were repeatedly reactive. Of the 42 HIV-2 EIA repeatedly reactive specimens, 40 were confirmed positive for HIV-1. Two specimens required testing with an investigational HIV-2 Western blot. Both specimens were indeterminate on the HIV-2 Western blot. Therefore, the Genetic Systems HIV-1/HIV-2 Peptide EIA detected all HIV confirmed positives in high risk populations from the United States.

Comparative sensitivity of the Genetic Systems HIV-1/HIV-2 Peptide EIA to a previously licensed test for antibody to HIV-1 and HIV-2 was evaluated in paired tests on U.S. high risk subjects (n = 1080), or known positive specimens from U.S. (n = 505) and non-U.S. origin (n = 331). In these studies, the Genetic Systems HIV-1/HIV-2 Peptide EIA was reactive for 895 of 895 subjects who had positive HIV-1/HIV-2 screening test results which had additionally been confirmed by HIV-1 Western blot.

Reactivity with HIV-1 Seroconversion Panels

The Genetic Systems HIV-1/HIV-2 Peptide EIA detected the presence of antibody to HIV-1 in specimens from sixteen commercially available HIV-1 seroconversion panels as early as, or earlier than, a licensed HIV-1/HIV-2 EIA, and licensed HIV-1 Western blot. Reactivity demonstrated using one lot (343KP1) of the Genetic Systems HIV-1/HIV-2 Peptide EIA with 16 seroconversion panels is shown in Table 5 below. (Note: Only bleeds before and after the point of seroconversion are presented.)

Table 5: Detection of Antibody to HIV-1 in Seroconversion Panels

Panel	Date of Bleed	Genetic Systems HIV-1/HIV-2 Peptide EIA	Licensed HIV-1/HIV-2 EIA	Licensed HIV-1 Western blot
PRB903	07/23/85	NR	NR	NEG
	07/25/85	NR	NR	IND
	07/30/85	R	NR	POS
	08/01/85	R	NR	POS
	08/06/85	R	R	POS
	08/08/85	R	R	POS
PRB904	06/17/81	NR	NR	NEG
	07/30/81	R	R	POS
	08/06/81	R	R	POS
PRB905	07/07/81	NR	NR	IND
	07/14/81	NR	NR	IND
	08/18/81	R	R	POS
PRB908	02/08/89	NR	NR	NEG
	02/10/89	R	R	POS
PRB909	01/23/89	NR	NR	NEG
	01/30/89	NR	NR	NEG
	02/06/89	R	R	POS
	02/08/89	R	R	POS
PRB910	05/11/89	NR	NR	NEG
	05/25/89	NR	NR	NEG
	06/06/89	R	R	POS
	06/08/89	R	R	POS
PRB911	12/28/89	NR	NR	NEG
	01/02/90	NR	NR	IND
	01/04/90	NR	NR	IND
	01/09/90	R	R	POS
	01/11/90	R	R	POS
PRB912	02/14/90	NR	NR	NEG
	02/23/90	R	R	POS
PRB913	09/17/81	NR	NR	NEG
	10/09/81	R	R	POS
PRB914	01/12/90	R	NR	IND
	01/16/90	R	R	POS
	01/19/90	R	R	POS
PRB916	07/25/89	NR	NR	NEG
	08/09/89	R	R	POS
	08/14/89	R	R	POS
PRB917	12/14/90	NR	NR	IND
	12/19/90	R	NR	IND
	12/21/90	R	NR	IND
	12/26/90	R	R	POS

Panel	Date of Bleed	Genetic Systems HIV-1/HIV-2 Peptide EIA	Licensed HIV-1/HIV-2 EIA	Licensed HIV-1 Western blot
PRB918	02/22/91	NR	NR	NEG
	02/27/91	R	NR	IND
	03/05/91	R	R	POS
	03/07/91	R	R	POS
PRB921	07/14/89	NR	NR	NEG
	07/17/89	NR	NR	NEG
	07/21/89	R	NR	POS
	07/26/89	R	R	POS
	07/28/89	R	R	POS
	07/31/89	R	R	POS
PRB922	08/07/93	NR	NR	NEG
	08/11/93	NR	NR	NEG
	08/14/93	R	NR	NEG
	08/18/93	R	NR	POS
PRB924	12/13/93	NR	NR	NEG
	12/15/93	R	NR	NEG
	12/20/93	R	NR	POS

Reactivity in Preselected Specimens from Individuals Positive for HIV-2 Antibodies and Confirmed by Western Blot

A total of 336 specimens, obtained from HIV-2 confirmed antibody positive individuals, were tested with Genetic Systems HIV-1/HIV-2 Peptide EIA. All specimens were found to be repeatedly reactive with a licensed HIV-1/HIV-2 EIA and a licensed HIV-2 EIA. Of the 336 specimens tested, all (100%) were repeatedly reactive with Genetic Systems HIV-1/HIV-2 Peptide EIA; 205 of these specimens were confirmed as positive for antibody to HIV-1 and HIV-2 by Western blot; 131 specimens were positive on an investigational HIV-2 Western blot. (Out of the 131, 127 were indeterminate and 4 were negative on a licensed HIV-1 Western blot.)

The HIV-2 sensitivity of the Genetic Systems HIV-1/HIV-2 Peptide EIA was determined by comparison with a previously licensed test for antibody to HIV-1/HIV-2 and a previously licensed test for antibody to HIV-2. All of the assays detected 336 of 336 samples which were additionally confirmed by a positive investigational HIV-2 Western blot, for an estimated sensitivity of 100% (95% confidence interval: 99.85-100%) compared with Western blot.

Reactivity in Populations from an HIV-2 Endemic Area

The ability of the Genetic Systems HIV-1/HIV-2 Peptide EIA to detect antibodies to HIV-2 in specimens from an HIV-2 endemic area is shown in Table 6. The data include the following: 100 serum samples obtained from women attending a family planning clinic in Senegal; 617 serum samples collected from healthy adults and clinic patients in rural and urban areas of Liberia; 589 serum samples collected from low and high risk groups (including commercial sex workers) in Sierra Leone; and 287 serum samples collected prospectively in Côte d'Ivoire (risk group unknown). All samples were tested in parallel with a licensed

HIV-1/HIV-2 EIA. The samples from Senegal, Sierra Leone, and Liberia were also tested in parallel with a licensed HIV-2 EIA. Specimens from Côte d'Ivoire were tested with an investigational HIV-2 Western blot. Samples repeatedly reactive with the Genetic Systems HIV-1/HIV-2 Peptide EIA or the licensed HIV-1/HIV-2 EIA or HIV-2 EIA were tested with a licensed HIV-1 Western blot and an investigational HIV-2 Western blot. If the sample volume was not sufficient for testing with a licensed HIV-1 Western blot, it was tested with a licensed HIV-1 IFA.

Table 6: Detection of Antibodies to HIV-2 in Specimens from an Endemic Area

Results with HIV-1/HIV-2 Peptide EIA			Licensed HIV-1/HIV-2 EIA	Licensed HIV-2 EIA	Repeatedly Reactive Specimens		
Endemic Area	No. Tested	Repeatedly Reactive	Repeatedly Reactive	Repeatedly Reactive	Pos. by HIV-1 Western blot, or IFA alone	Pos. by HIV-2 Western blot alone	Pos. by Both HIV-1 and HIV-2 Western Blot
Senegal	100	3	1	2	1	0	0
Liberia	614[a]	46	*	*	2	3	0
Sierra Leone	589	66	75	84	28	5	4
Côte d'Ivoire	287	36	36	NT	17	3	7
TOTAL	1590	151	112	86	48	11	11

* Samples were initially reactive on the licensed HIV-1/HIV-2 EIA (n = 133) and the licensed HIV-2 EIA (n = 124). There was insufficient volume for retesting.

[a] A total of 617 specimens were tested. However, 1 specimen was unresolved for HIV-1 and 2 specimens were unresolved for HIV-2. Therefore, these 3 specimens are not included in the total numbers. Two of the specimens were initially reactive with the licensed HIV-1/HIV-2 EIA and all three specimens were initially reactive with the licensed HIV-2 EIA

Specimens were considered positive by HIV-2 Western blot if two of the following three bands were present: gp105/140, gp36/41, or p26. Specimens were considered positive by HIV-1 Western blot if two of the following three bands were present: gp120/160, gp41, or p24. A test specimen is interpreted as positive by licensed IFA when there is a specific cytoplasmic staining pattern in the HIV-1 infected cells and there is a significant difference in the intensity of fluorescent staining and the pattern of fluorescence between the HIV-1 infected and uninfected cells.

In this study, 9.5% (151/1590) of the specimens from West African populations that were tested by Genetic Systems HIV-1/HIV-2 Peptide EIA were repeatedly reactive. All of the specimens were also tested with a licensed HIV-1/HIV-2 EIA. One hundred twelve (112) specimens (7.0%) were repeatedly reactive. Specimens from Côte d'Ivoire were not tested with a licensed HIV-2 EIA but all were tested with an investigational HIV-2 Western blot. All specimens from Senegal, Liberia, and Sierra Leone were tested with a licensed HIV-2 EIA (a total of 1303 specimens). Of the 1303 specimens tested, 86 specimens (6.6%) were repeatedly reactive on a licensed HIV-2 EIA.

All specimens testing repeatedly reactive by the Genetic Systems HIV-1/HIV-2 Peptide EIA, licensed HIV-1/HIV-2 EIA and the licensed HIV-2 EIA were tested with a licensed HIV-1 Western blot or licensed HIV-1 IFA and an investigational HIV-2 Western blot, using the criteria given previously. All specimens positive by Western blot (48 specimens that were positive by HIV-1 Western blot, 11 specimens that were positive by HIV-2 Western blot, and 11 specimens that were positive by both HIV-1 and HIV-2 Western blot) and repeatedly

reactive by a licensed HIV-1/HIV-2 EIA and/or licensed HIV-2 EIA were also repeatedly reactive by Genetic Systems HIV-1/HIV-2 Peptide EIA.

In addition, comparative sensitivity with a licensed HIV-1/HIV-2 EIA was evaluated in prospective studies in endemic areas of West Africa (Senegal, Liberia, Sierra Leone, Côte d'Ivoire). In these studies, the Genetic Systems HIV-1/HIV-2 Peptide EIA was positive in 22 of 22 samples which were reactive by the licensed HIV-1/HIV-2 EIA and additionally confirmed by a positive investigational HIV-2 Western blot, demonstrating equivalent sensitivity for detection of antibody to HIV-2 compared with a previously licensed test.

VI. PACKAGE INSERT

A copy of the package insert (directions for use) is attached.

SBA (95-0794)

Licensing Review Committee:

Subhash Dhawan, Ph.D., Chairperson

Indira Hewlett, Ph.D., Co-Chairperson

Gary Riordan

Robert Boykins

Vance Berger, Ph.D.

FINDING OF NO SIGNIFICANT IMPACT
FOR
APPROVAL OF PRODUCT AND ESTABLISHMENT LICENSE APPLICATION
SUPPLEMENTS FOR THE MANUFACTURE OF
HUMAN IMMUNODEFICIENCY VIRUS TYPES 1 AND 2 (SYNTHETIC PEPTIDE)
(i.e., GENETIC SYSTEMS HIV-1/HIV-2 PEPTIDE EIA)
TO
GENETIC SYSTEMS CORPORATION

The review committees have carefully considered the potential environmental impact of these approval actions and have concluded that the Environmental Assessment Report submitted by Genetic Systems Corporation for Human Immunodeficiency Virus Types 1 and 2 (Synthetic Peptide) is accepted based on the following:

No significant adverse environment effect/risk is expected to result from the production or use of this product. The manufacture and distribution of the product does not generate or emit pollutants or materials considered to be biohazardous. Only non-hazardous materials are released into sewer systems. All other waste materials are disposed of in accordance with federal, regional and local environmental requirements.

Therefore, the committees find no significant impact on the environment as a result of these approval actions.

7-24-97
Date

Howard S Balick
Environment Assessment PLA Supplement Reviewer

7/24/97
Date

Robert Davis
Environment Assessment ELA Supplement Reviewer

Concurrence:

7/31/97
Date

Mary Lou Ackerson
Director
Division of Blood Applications

7/31/97
Date

John A Eltinge Jr
Director
Division of Establishment Licensing